2013-1306

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

BRISTOL-MYERS SQUIBB COMPANY,

Plaintiff-Appellant,

v.

TEVA PHARMACEUTICALS USA, INC.,

Defendant-Appellee.

Appeal from the United States District Court for the District of Delaware in No. 10-CV-0805, Judge Christopher J. Burke.

BRIEF FOR PLAINTIFF-APPELLANT BRISTOL-MYERS SQUIBB COMPANY

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June 3, 2013

CERTIFICATE OF INTEREST

Counsel for Bristol-Myers Squibb Company certifies as follows:

1. The full name of every party or amicus represented by us is:

Bristol-Myers Squibb Company

2. The name of the real party in interest (if the party named in the caption is not the real party in interest) represented by us is:

Not applicable.

3. All parent corporations and any publicly held companies that own 10 percent or more of the stock of the party or amicus curiae represented by us are:

None.

4. The names of all law firms and the partners or associates that appeared for the parties represented by us in the trial court, or are expected to appear in this Court, are:

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STATEMENT OF RELATED CASES

No appeal in this case was previously before this Court or any other appellate court. Counsel for Plaintiff-Appellant Bristol-Myers Squibb Company ("BMS") are aware of no other case pending in this or any other court that would directly affect or be directly affected by the Court's decision in this appeal.

STATEMENT OF JURISDICTION

The district court had jurisdiction pursuant to 28 U.S.C. §§ 1331 and 1338. It entered a final judgment on March 5, 2013. A172. BMS timely appealed. A6096. This Court has jurisdiction pursuant to 28 U.S.C. § 1295(a)(1).

STATEMENT OF ISSUE

Whether the district court erred in concluding that claim 8 of U.S. Patent No. 5,206,244 ("the '244 patent") is invalid as obvious.

INTRODUCTION

BMS is unaware of any case in which this Court has invalidated as obvious a claim to a new chemical compound that possesses unexpected therapeutic properties. Yet the district court did exactly that here: despite finding that the claimed compound (entecavir) has several *unexpected* therapeutic properties, the court determined that a skilled artisan would have had a reasonable *expectation* of success in obtaining the claimed invention. That error, along with the court's

improper reliance on hindsight and dismissal of its own findings of several objective indicia of nonobviousness, requires reversal of the invalidity judgment.

Claim 8 of the '244 patent is directed to the chemical compound entecavir, the active ingredient in BMS's hepatitis B drug Baraclude®. At the time of entecavir's invention in 1990, there was no FDA-approved treatment for hepatitis B. By the time of Baraclude®'s launch in 2005, the FDA had approved other hepatitis B treatments, but they all had significant shortcomings, including serious side effects and high rates of viral resistance. BMS's discovery of entecavir solved those problems. As the district court found, entecavir possesses several unexpected properties critical to its antiviral efficacy and safety, including "'extraordinary potency against' the hepatitis B virus," "a very high genetic barrier to resistance," and "a large therapeutic window" between the low doses necessary to treat hepatitis B and the high doses that can cause toxicity. A150-151. And contrary to the purported expectation that entecavir would have "similar properties to 2'-CDG" (A128), an extremely toxic prior art compound on which Teva based its obviousness theory, entecavir is exceptionally safe. As a result of its antiviral efficacy and safety, Baraclude® has enjoyed enormous success in the marketplace.

Despite entecavir's demonstrated therapeutic and commercial success as a treatment for hepatitis B, the district court held claim 8 invalid as obvious. But the court's ultimate conclusion of obviousness, which must be supported by clear and

convincing evidence, cannot be reconciled with its own finding that entecavir possesses several unexpected therapeutic properties. This Court and its predecessor have long recognized that "a compound and all of its properties are inseparable" for purposes of evaluating obviousness. *In re Papesch*, 315 F.2d 381, 391 (C.C.P.A. 1963). *Unexpected* properties that go to the core of the claimed invention are accordingly inconsistent with the reasonable *expectation* of success necessary to prove obviousness. Indeed, where "the success was finding a compound that had high activity, few side effects, and lacked toxicity," there can be no reasonable expectation of success if, as the district court found here, those properties were unexpected. *Yamanouchi Pharm. Co. v. Danbury Pharmacal, Inc.*, 231 F.3d 1339, 1345 (Fed. Cir. 2000).

The district court also improperly engaged in a hindsight-driven analysis to conclude that a skilled artisan would have successfully navigated a maze of complex choices along the path to creating entecavir. Even the court's selection of the prior art compound 2'-CDG as a lead compound was made with the inventors' discovery in mind, impermissibly focusing on the structural similarities between 2'-CDG and entecavir. And many of the prior art references relied upon by the district court actually teach away from the claimed invention, requiring several counterintuitive choices to arrive at entecavir. From the selection of a lead compound through the choice of precisely where and how to modify its structure,

the district court's own analysis confirms that each of those decisions involved a choice among many reasonable possibilities, where even small changes could produce significant differences in biological activity. The unpredictable outcomes at each step quickly multiply into countless possibilities for a skilled artisan to consider, which is far from clear and convincing proof of obviousness. Instead, as this Court has recently observed, the type of analysis employed by the district court here is "a poster child for impermissible hindsight reasoning." *Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1296 (Fed. Cir. 2012).

To guard against precisely such hindsight reasoning, this Court requires consideration of objective indicia of nonobviousness in every case. But the district court committed several legal errors on this front as well. The court improperly compared entecavir's unexpected results to tenofovir, a subsequently-approved hepatitis B therapy that was never asserted as part of any prior art obviousness combination, and also impermissibly relied on the inventor's own insights. Moreover, despite finding several objective indicia of nonobviousness (*i.e.*, unexpected results, long-felt but unmet need, and commercial success), the court improperly dismissed those findings as negated by a perceived weaker showing on other objective factors (*i.e.*, skepticism and failure of others). That was error because, as this Court has long recognized, even a single objective factor can demonstrate nonobviousness. Had the court properly "considered the objective

evidence in its entirety before making an obviousness finding, and considered that evidence in light of the actual burden imposed," *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1080 (Fed. Cir. 2012), it could not have found clear and convincing proof of obviousness.

The invalidity judgment should be reversed and the case remanded for further proceedings relating to remedies in the district court.

STATEMENT OF CASE

On June 14, 2010, Teva filed an Abbreviated New Drug Application ("ANDA") seeking FDA approval to market a generic version of Baraclude®. A2; A6082(¶1(i)); A6092(¶24). On September 22, 2010, BMS filed suit under the Hatch-Waxman Act, alleging that Teva's ANDA submission infringed the '244 patent under 35 U.S.C. § 271(e)(2) and that any commercial manufacture, use, offer for sale, or sale of Teva's generic product would similarly infringe. A6006-6007(¶¶29-30).

Teva stipulated to infringement to the extent the asserted claims were found valid and enforceable. A6082(¶1(iii),(iv)).[1] Teva contended, however, that claim 8 was invalid as obvious under 35 U.S.C. § 103 (A6055) and that the '244 patent was unenforceable due to inequitable conduct (A6064(¶7)).

[1] To narrow the issues in dispute, BMS withdrew its infringement contentions with respect to claims 1-6 and asserted only claim 8 at trial. A6094(¶38).

To allow for a trial and decision prior to the expiration of the 30-month stay on the approval of Teva's ANDA, the parties consented to have a magistrate judge conduct all proceedings in this case. A6085. In October 2012, the magistrate judge held a four-day bench trial on the issues of validity of claim 8 and enforceability of the '244 patent.

On February 11, 2013, the magistrate judge issued an opinion setting forth the court's findings of fact and conclusions of law. *Bristol-Myers Squibb Co. v. Teva Pharm. USA, Inc.*, ___ F. Supp. 2d ___, 2013 WL 509152 (D. Del. Feb. 11, 2013) (A1-171). The court concluded that claim 8 is invalid as obvious (A153) but rejected Teva's claim of inequitable conduct (A170-171).

The court entered final judgment on March 5, 2013. A172. BMS timely appealed. A6096. Teva has not appealed from the judgment of no inequitable conduct.

STATEMENT OF FACTS

A. The '244 Patent

The '244 patent is titled "Hydroxymethyl (Methylenecyclopentyl) Purines and Pyrimidines" and names two former BMS scientists, Drs. Robert Zahler and William Slusarchyk, as inventors. BMS's predecessor (E.R. Squibb & Sons, Inc.) filed the application for the '244 patent on September 20, 1991. A190. The application claims priority to a related application filed on October 18, 1990. *Id.*;

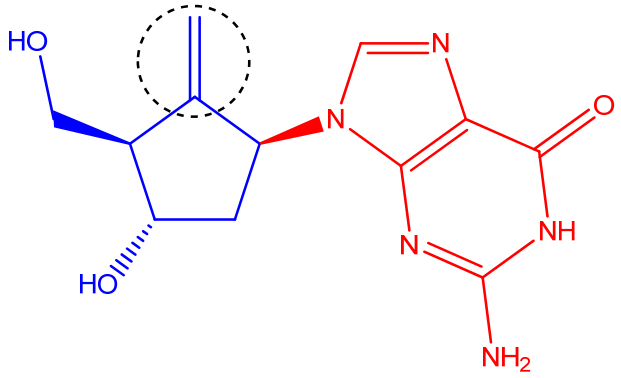
see also A5(¶¶8-9); A91. The '244 patent issued on April 27, 1993 (A190), and expires on February 21, 2015 (A8(¶17)), thereby providing ten years of effective patent life from Baraclude®'s initial approval on March 29, 2005 (A3-4(¶¶2-3)).

The '244 patent discloses and claims a genus of chemical compounds from the broader class of compounds known as "nucleoside analogs." A191-192; A217-218; *see also* A8(¶18). The specification teaches that the claimed compounds "are antiviral agents that can be used to treat viral infection in mammalian species such as … humans." A192(3:62-66). The specification further states that the claimed compounds "are also believed to be active against a variety of other DNA and retroviruses," including "hepatitis B virus." A192(4:34-41).

Claim 8 is specifically directed to the compound entecavir, which has the chemical name:

> [1S-(1α,-3α,4β)]-2-amino-1,9-dihydro-9-[4-hydroxy-3-(hydroxymethyl)-2-methylene-cyclopentyl]-6H-purin-6-one.

A218. The chemical structure for entecavir includes a five-membered carbocyclic ring (shown in blue) and a guanine base (shown in red):



entecavir

A11. The guanine base is one of the nucleobases that occurs naturally in DNA and RNA. A8-9(¶¶20-21). Entecavir's carbocyclic ring has been modified to include an "exocyclic methylene group" (shown inside the dotted circle above),[2] which is a group containing a carbon-carbon double bond, attached at the top position of the ring. A9-10(¶¶22,25). This top position is commonly referred to as either the 5'- or 6'-position of the carbocyclic ring. A9 n.6; A1009(33:18-22); A1078(307:7-12); A1136(535:2-17).[3]

[2] The chemical structures in this brief follow the convention of representing carbon atoms and hydrogen atoms bonded to carbon without labels.

[3] For consistency with the nomenclature of natural nucleosides, this brief refers to the top position in a five-membered carbocyclic ring as the 6'-position.

B. The Prior Art

1. Three broad classes of nucleoside analogs were known in the art.

Natural nucleosides (*e.g.*, adenosine, guanosine, cytidine, thymidine, and uridine) are the basic building blocks of DNA and RNA. A8-9(¶¶20-21). They are chemical compounds made up of a sugar and a base. A8-9(¶20).

Nucleoside analogs, such as entecavir, are compounds that have been designed by chemists to mimic natural nucleosides in some way, but their chemical structure has been modified from their naturally-occurring counterparts. A8(¶19); A1035(136:18-137:12). Even small modifications in chemical structure can result in nucleoside analogs that differ significantly from the natural nucleosides they are intended to mimic, as well as from other nucleoside analogs. *E.g.*, A1041(160:15-161:15); A1204(805:10-15).

Nucleoside analogs can interfere with the replication of viral DNA—a critical step in viral reproduction—and may therefore be useful as antiviral drugs. A8(¶19). A significant difficulty in developing antiviral drugs based on nucleoside analogs, however, is that these compounds often also interfere with the replication of human DNA, which causes toxicity. *E.g.*, A1208(821:6-822:6); A2028(1:29-33) ("[F]ew [nucleoside analogs] have good activity against the virus without untoward side effects."). As a result, even nucleoside analogs that initially showed promise as antiviral agents have been abandoned due to their toxicity. *E.g.*,

A1208(821:6-822:6) (lobucavir); A1255-1256(1010:22-1012:11) (fialuridine). Nucleoside analog research has thus been an active but risky area of drug discovery, as scientists continue to look for compounds that have potent antiviral activity but are not toxic to humans.

At the time of entecavir's invention in 1990, three broad classes of nucleoside analogs were known in the art: furanosides, acyclics, and carbocyclics. A18(¶48); A1041(158:11-160:1).

a. Furanosides had long been known as safe and effective antiviral agents.

Furanosides are nucleoside analogs that retain the sugar, or "furanose," ring present in natural nucleosides, but they have been modified by different substitutions to the base and/or sugar. A18-19(¶¶48-50); A1041(160:2-161:15); A1195(768:20-769:2).

Furanosides have been studied as potential drugs since at least the late 1950s and have long been known to possess potent biological activity. A18(¶49). By the time of entecavir's invention in 1990, there were a large number of furanosides known in the art, and the earliest FDA-approved antiviral nucleoside analogs came from this class of compounds. A18(¶49); A19(¶51); A1045(176:5-14); A1196(773:23-774:1). It was also well known that furanosides are not difficult to synthesize. A19(¶50); A1196(773:23-24); A1283(1115:6-9).

b. Acyclics had set the standard for antiviral potency.

Acyclics are nucleoside analogs that lack the closed, cyclic sugar ring generally found in natural nucleosides. A1041-1042(161:19-162:13). They have a non-cyclic chain of atoms in place of the sugar ring and can also have different substitutions to the chain and/or base. A1041-1042(161:19-163:20).

By the time of entecavir's invention in 1990, there were a large number of acyclics known in the art, and many were known to have potent antiviral activity. A19(¶53); A1041-1042(161:19-164:5). Compounds from this class of nucleoside analogs, including acyclovir and ganciclovir, were frequently used as the standards against which to measure the antiviral activity of newly-developed compounds. A1282(1112:16-1113:4) (acyclovir and ganciclovir "had set the standard" for antiviral activity); *see also* A1210(829:2-4) (acyclovir); A2207 (acyclovir and ganciclovir); A2068 (acyclovir); A2149-2150 (acyclovir and ganciclovir (DHPG)). By 1990, acyclovir was already approved by the FDA for the treatment of herpes infections, and ganciclovir was in advanced clinical studies on its way to FDA approval. A19(¶¶52,55); A1042(162:9-13); A1196(772:2-10). Acyclovir was such an important development in the treatment of herpes that its inventors were awarded the Nobel Prize in 1988. A1282(1113:7-12). Like furanosides, acyclics were known to be easy to synthesize. A19(¶53); A1196(773:19-23); A1283(1114:16-19).

c. Carbocyclics had not resulted in any FDA-approved drugs despite decades of research.

Carbocyclics, such as entecavir, are nucleoside analogs that contain a three-, four-, or five-membered ring composed entirely of carbon atoms in place of the sugar ring found in natural nucleosides. A20(¶57); A1043(166:21-167:15); A1084(331:10-21); A1147(578:5-8); A1159(626:17-20). Carbocyclics may also contain various substitutions to the ring and/or base portions of the compound. *E.g.*, A2102-2105 (listing examples).

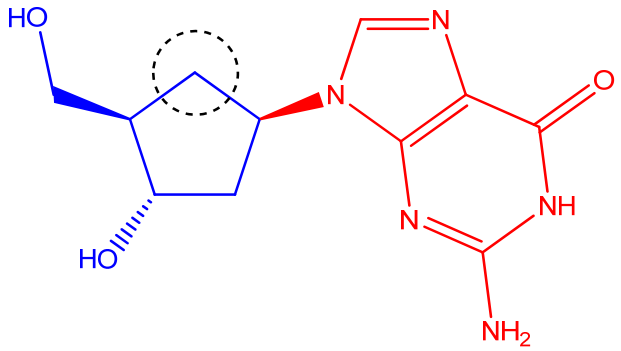
By the time of entecavir's invention in 1990, there were hundreds of carbocyclics known in the art. *E.g.*, A2102-2105 (disclosing 120 carbocyclics); A2144-2152 (disclosing 60 carbocyclics); *see also* A25(¶74) (noting the "large number of different carbocyclic purine nucleosides" disclosed in the prior art). Many of those compounds were known not to have any antiviral activity,[4] and there were no FDA-approved carbocyclics at the time of entecavir's invention. A20(¶59); A1283(1114:1-3).

[4] *E.g.*, A2107 ("C-Ado showed no significant antiviral activity against HSV, vaccinia, rhino, or influenza viruses."); A2111 (compound 47a was "devoid of antiviral activity"); A2114 (compounds 64a and 65a "were ineffective as either antitumor or antiviral agents"); A2147 (C-Guo, C-8-AzaGuo, and C-6-ThioGuo are "inactive"); A2150 ("[T]he carbocyclic analog … of 2',3'-dideoxyadenosine is inactive."); A2151 ("Carbocyclic uridine or 3'-deoxyuridine analogs with hydrogen, halogen, or other substituents at the 5-position of the pyrimidine ring … were all inactive.").

It was also known in the art that even small changes to the structure of a carbocyclic compound could have significant effects on a compound's biological activity. *E.g.*, A2003 (noting that compound 24 was nine times less active against herpes simplex virus than compound 10, which has the *same* chemical formula but differs only in the spatial orientation of a single fluorine atom); A2091 (describing the "noteworthy" effect of substituting a single fluorine atom, which created a compound with "unprecedented biological activity," particularly as compared with the "much less active" parent compound). And, unlike furanosides or acyclics, carbocyclics were known to be difficult to synthesize. A20(¶60); A1283(1114:4-1115:9).

2. 2'-CDG was one of hundreds of carbocyclics known in the art.

In the mid-1980s, Dr. Y. Fulmer Shealy published an article ("the Shealy article") and obtained U.S. Patent No. 4,543,255 ("the Shealy patent") describing the synthesis and antiviral activity of several carbocyclics. A2071-2076; A2077-2085. In 1984, Dr. Shealy first disclosed the carbocyclic compound known as 2'-CDG:



2'-CDG

A2072 (compound 12); *see* A23-25(¶¶69,73). As illustrated above, 2'-CDG includes a guanine base (shown in red) and a carbocyclic ring (shown in blue). 2'-CDG differs from the natural nucleoside 2'-deoxyguanosine because it contains a carbon atom in place of the oxygen atom at the top of the sugar ring (shown in the dotted circle). A23(¶69).

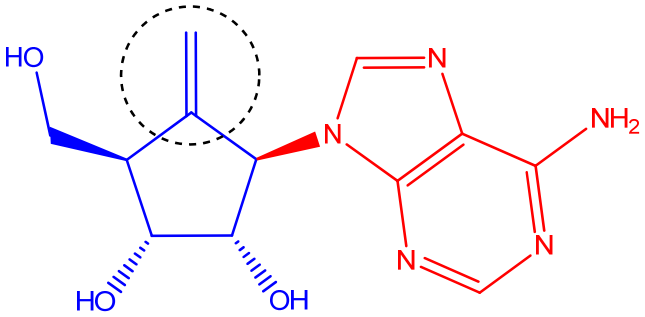
That small change had a significant effect on the compound's biological activity. Scientists recognized in the 1980s that 2'-CDG demonstrated "very good" activity against the herpes virus. A24(¶70). By 1990, however, several other carbocyclics were known to have significantly better antiviral activity than 2'-CDG. *E.g.*, A2091 (describing the "unprecedented biological activity" of a new carbocyclic and finding it "noteworthy" that 2'-CDG is "much less active against herpes simplex *in vitro*"); A2149 (Fig. 4) (showing that the carbocyclic C-DAPdR (compound 44) is twice as potent as 2'-CDG).

Although scientists initially believed that 2'-CDG might not be toxic (A2086), those same scientists soon discovered that 2'-CDG is extremely toxic and

published their findings in the early 1990s. A2057; A2064. And using woodchucks, which are often used to study hepatitis B because they carry a form of the virus similar to that which infects humans (A1118(462:10-21)), other scientists "never found a dose [of 2'-CDG] that wasn't toxic." A1255(1009:18-1010:9). As a result, 2'-CDG has never been tested in humans. A1255(1010:12-17).

3. The only prior art compound containing an exocyclic methylene group at the 6'-position was the highly toxic Madhavan compound 30.

In 1988, Dr. G.V. Bindu Madhavan published an article ("the Madhavan article") describing work done with derivatives of a naturally-occurring carbocyclic nucleoside known as aristeromycin. A2001; *see also* A41(¶114). One of the compounds studied was compound 30:



Madhavan compound 30

A2002. Compound 30 has an adenine base (shown in red) and a carbocyclic ring (shown in blue) that has been modified to include a carbon attached by a double-

bond at the 6'-position (*i.e.*, an exocyclic methylene group) (shown in the dotted circle). A41(¶114).

Although nucleoside analogs with an exocyclic methylene group substituted at other locations were known in the prior art (*e.g.*, A2008; A2025), the Madhavan article is the only prior art reference that discloses an exocyclic methylene group at the 6'-position of a carbocyclic ring. A169; A1078(308:13-309:1); A1207(815:21-816:9). But the Madhavan article also teaches that this substitution is associated with increased toxicity. Of the compounds that Dr. Madhavan studied for antiviral activity, compound 30 was "[t]he most potent, but also the most toxic," while compound 10 (which has a fluorine atom instead of a methylene group at the 6'-position) was "nearly as active and much less toxic." A2003. Dr. Madhavan thus concluded that the potent antiviral activity of compounds like compound 30 was due to their toxicity to the host cell, rather than "a direct inhibitory effect on viral growth." *Id.*

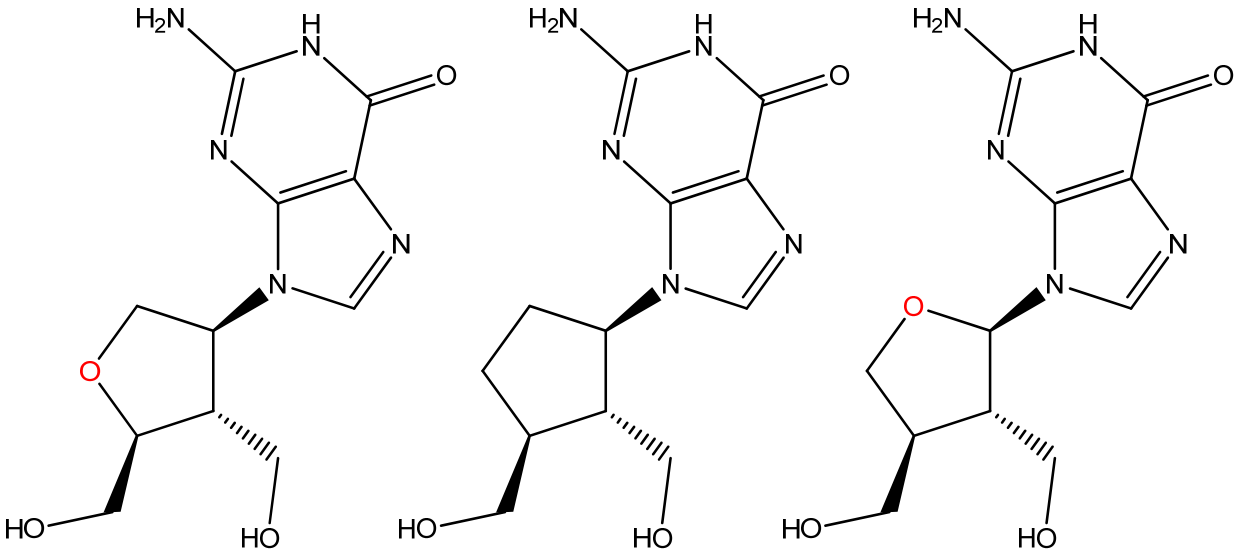
C. BMS's Discovery Of Entecavir From Acyclic And Furanoside Lead Compounds

In 1985, a team of BMS scientists led by Dr. Robert Zahler began studying nucleoside analogs to develop new antiviral therapies. A12-13(¶33); A1194(763:12-764:17). Dr. Zahler selected acyclovir (an acyclic) as the lead compound for his group's research because of the drug's proven safety, efficacy, and ease of synthesis. A13(¶34); A1196(771:20-772:10, 773:19-774:20). Over the

course of the following year, Dr. Zahler's team synthesized 30 to 40 acyclics, but none demonstrated sufficient antiviral activity to warrant further development. A13(¶34); A1197(776:20-777:6); A1198(779:8-780:13).

Dr. Zahler next focused on oxetanocin-A (a furanoside) as a lead compound. A1203(800:11-801:16); A2217. Based on the antiviral activity of oxetanocin-A, Dr. Zahler's team synthesized the analogous carbocyclic compound lobucavir, which turned out to have strong antiviral activity. A1223-1224(882:20-883:21); A1226-1227(891:3-896:17); A2207; A2217.

After their invention of lobucavir, Dr. Zahler's team continued to search for new antiviral nucleoside analogs and synthesized several compounds with slightly different structures, including the closely-related compounds SQ-33796, SQ-34355, and SQ-34170:



SQ-33796 (active) SQ-34355 (inactive) SQ-34170 (inactive)

A1204(804:9-805:9); A2218. Those compounds differed only by the presence and location of a single oxygen atom on the sugar ring (shown in red). That small change, however, resulted in significant differences in their biological activity. Dr. Zahler found that SQ-33796 had "quite promising" antiviral activity, but that SQ-34355 and SQ-34170 were inactive. A1204(804:9-805:16); A2218.

To understand this difference, Dr. Zahler and his team used computational modeling techniques—which were not commonly used in drug discovery at the time—to compare the three-dimensional structures of those compounds. A1204-1205(805:17-808:16). They discovered that SQ-33796 adopts a preferred three-dimensional shape similar to lobucavir, but that SQ-34355 and SQ-34170 do not. A1205(808:5-16). Dr. Zahler hypothesized that designing compounds to adopt three-dimensional shapes similar to lobucavir would lead his team to more potent antiviral compounds. A1205(808:17-810:22); A2219.

Following that unconventional hypothesis, Dr. Zahler conceived of the structure for entecavir. A102 n.18; A1208(820:16-22); A2220. After computational modeling confirmed that entecavir had the three-dimensional shape that Dr. Zahler intended, Dr. Zahler's team attempted to synthesize entecavir. A1207(816:21-818:3). The synthesis was difficult, but after six months they were finally able to produce entecavir. A1208-1209(822:7-823:15).

Similarity in three-dimensional shape to lobucavir, however, was no guarantee that entecavir would be safe and effective. In fact, although lobucavir has potent antiviral activity, it ultimately failed in clinical studies after it was found to be carcinogenic. A1208(821:6-822:6); A2232.

Dr. Zahler's team tested entecavir against the herpes virus, but found that it was about fourfold less active against herpes than acyclovir. A16(¶41); A1210(827:20-828:5). As a result, they decided that entecavir was not potent enough to warrant further development as an antiherpetic compound. A16(¶41); A1210(828:16-829:9). Dr. Zahler did not initially test entecavir for activity against the hepatitis B virus because BMS did not have a hepatitis B assay at that time. A16(¶41); A1210(828:6-15).

BMS ultimately developed such an assay in 1994, and Dr. Zahler handpicked entecavir as one of twenty compounds to be tested. A1210(829:10-830:16). Surprisingly, entecavir showed extremely high potency and selectivity for hepatitis B. A1211-1212(833:7-838:4); A2233. BMS then put entecavir into clinical development, and in 2005, after several years of clinical testing, the FDA approved BMS's drug Baraclude®, which contains entecavir as its active ingredient, as a treatment for chronic hepatitis B in adults. A11(¶28); A1212-1213(838:20-839:2).

D. Entecavir's Use Against Hepatitis B

At the time of entecavir's invention in 1990, hepatitis B was the "chief cause" of cirrhosis and liver cancer and the "ninth major cause of death worldwide," leading physicians to conclude that "chronic hepatitis B virus (HBV) infection is the most important chronic viral infection affecting humans." A2209. But at that time, there was no FDA-approved treatment for hepatitis B. A147. The therapies that were approved before entecavir had major shortcomings, including high rates of drug resistance or serious side effects that only a small patient population could tolerate. A50(¶138); A59-60(¶¶168-169); A1107(418:5-419:16); A1339-1340(1339:14-20, 1341:15-1342:2).

Entecavir unexpectedly solved those problems. It is by far the most potent drug gram-for-gram ever discovered for the treatment of hepatitis B. A1343-1344(1357:12-1360:17). While other hepatitis B drugs require doses of 20-600 milligrams per day, entecavir is effective at doses as low as 0.5 milligrams per day. A1344(1358:20-1360:17); A2255; A2256. As the district court found, a person of ordinary skill in the art would not have expected entecavir's "'extraordinary potency against' the hepatitis B virus." A150.

Entecavir's high potency reduces exposure to the drug, providing less opportunity for the hepatitis B virus to mutate and develop drug resistance. A49(¶136); A1345-1346(1365:11-1366:13). Entecavir also inhibits viral

replication in three different ways, again making it more difficult for resistant mutant strains to develop. A1345(1365:16-1367:6). As a result, only 1.2% of patients who have not previously received a nucleoside-based treatment for hepatitis B develop resistance after six years of treatment with entecavir. A49(¶137); A1346(1367:7-19). By comparison, patients on therapies that came to market before entecavir developed resistance at very high rates (up to 70%). A50(¶138). The district court found that entecavir's "very high genetic barrier to resistance" is one of entecavir's unexpected therapeutic properties. A151.

Entecavir provides these clinical benefits while remaining an exceptionally safe drug. A50-51(¶140); A1114(446:1-7). Because entecavir is highly selective for the hepatitis B virus, it has an unexpectedly broad therapeutic window, providing a wide gap between the low doses of the drug that are effective against hepatitis B and the high doses that could cause unwanted toxicity. A50-51(¶140); A151; A1211(833:7-24); A1277(1097:7-1098:6). That high selectivity for the target virus distinguishes entecavir from certain other antiviral nucleoside analogs, which have potent activity attributable to their general toxicity rather than their selective inhibition of viral replication. A1212(835:24-837:4).

Due to its exceptional potency, efficacy, and safety, entecavir has enjoyed enormous commercial success. Since the FDA's approval of Baraclude® in 2005, the drug has been prescribed hundreds of thousands of times in the United States

(A1323(1274:19-1275:18); A2259), generating over $835 million in domestic revenues through 2011 (A1323(1275:21-1276:17); A2258). Baraclude®'s worldwide sales are even greater, generating over $3.8 billion since its launch. A1323(1276:18-1277:16); A2257.

E. The District Court's Opinion

Following a four-day bench trial, the magistrate judge issued an opinion setting forth the court's findings of fact and conclusions of law. A1-171. The court ultimately concluded that claim 8 is invalid for obviousness, as detailed below.

1. Selection of a lead compound

The court's selection of a lead compound involved at least two distinct choices: (i) the selection of one of the three broad classes of nucleoside analogs known in the art—furanosides, acyclics, and carbocyclics; and (ii) the choice of a particular lead compound for further development.

As to the decision among the three broad classes of nucleoside analogs, the court quickly dismissed any consideration of furanosides and acyclics, which it acknowledged were well-known to have "good antiherpetic track records by the 1980s." A93-94. Instead, the court determined that a skilled artisan would have selected a carbocyclic as a lead compound because "carbocyclic analogs had generated excitement in the 1980s among researchers searching for compounds

with antiviral activity." A94. The court explained that, unlike the "crowded field[s]" of furanosides and acyclics—which had produced numerous potent antiviral compounds—carbocyclics remained a relatively untested field by the 1980s, which it believed made carbocyclics a "fertile place to begin in quests to discover new drugs." *Id.*

The court then determined that, having opted to work with carbocyclics, a person of ordinary skill in the art "would have targeted 2'-CDG as a 'natural choice for further development.'" A97 (citation omitted). The court relied on the fact that "medicinal chemists during the relevant time frame *were actually treating and using* 2'-CDG as a lead compound" (A97), the structural similarity between 2'-CDG and entecavir (A97-102), and 2'-CDG's antiviral activity (A103) to support its determination that 2'-CDG would have been selected as a lead compound. The court did not consider any other carbocyclics as potential leads—not even the several compounds identified to have superior antiviral activity to 2'-CDG in the very prior art references underlying the court's analysis. *See infra* pp. 44-45.

2. Modification of the lead compound

Starting from 2'-CDG as a lead compound, the court confronted four additional distinct decisions along the path of modifying 2'-CDG to obtain entecavir: (i) the choice between modifying 2'-CDG's carbocyclic ring and/or its

guanine base; (ii) the choice of which position on the carbocyclic ring to modify; (iii) the choice of which element to use to modify the carbocyclic ring; and (iv) the choice of what particular carbon-based group to add to the carbocyclic ring.

Addressing the choice between modifying 2'-CDG's carbocyclic ring and/or its guanine base, the court acknowledged that "[t]here appears to have been no reference in any prior art explicitly stating that changes to the guanine base must be avoided." A114. The court nevertheless determined that a skilled artisan would have elected to modify the carbocyclic ring because "the prior art did reflect that changes to 2'-CDG's sugar portion yielded compounds with increased activity (and, conversely, that changes to guanine bases of nucleoside analogs resulted in decreased activity)." *Id.* That determination is inconsistent with the numerous base-modified compounds with antiviral activity known in the prior art—including at least one such compound with superior activity to 2'-CDG. *See infra* pp. 48-49.

The court recognized that, having chosen to modify the carbocyclic ring rather than the base, a skilled artisan would then need to select which location on the carbocyclic ring to modify. A115. The court found that there was no clear choice of a single location to modify, but nonetheless determined that a person of ordinary skill in the art would focus on the 2'- and 6'-positions because they are "open positions where small changes could easily be made." *Id.*

After selecting the 2'- and 6'-positions to modify, the court acknowledged that a skilled artisan would still need to select a substituent to modify the lead compound. The court found that a person of ordinary skill in the art would look to the periodic table for guidance, focusing in particular on the top row because it contains the smallest atoms. A116-117. The court again acknowledged that there was no single obvious choice, but based upon testimony from Teva's expert Dr. Heathcock that carbon and fluorine would result in the most conservative changes, the court concluded that a skilled artisan would select one of those two elements to modify the 2'- or 6'-position of 2'-CDG. A117.

The court recognized that, even focusing entirely on carbon substitutions, a person of ordinary skill in the art would still need to select what type of carbon substitution to make. The court determined that a skilled artisan would select an exocyclic methylene group (*i.e.*, a carbon attached by a double bond) over a methyl group (*i.e.*, a carbon attached by a single bond) based on the relative size of those two groups, despite citing testimony from Teva's expert that a methyl group is only "a little bit bigger" than a methylene group (A1053(208:12-209:1)). A117 n.30. The court did not consider whether a skilled artisan might select one of the numerous other carbon-based substitutions disclosed in the prior art. *See infra* pp. 55-56.

Finally, having determined that a person of ordinary skill in the art would have chosen to add a fluorine or a carbon-based methylene group to the 2'- or 6'-position of 2'-CDG, the court concluded that those choices "equate to a small, finite number of changes to try to the lead compound," such that the claimed invention would have been obvious to try:

> Specifically, it would leave six options to pursue: binding a fluorine atom up or down at the 2 prime or [6] prime position and binding a double-bonded carbon atom at the 2 prime or [6] prime position.

A117. But in focusing on those six options, the court did not consider the many prior choices, and the significant number of options with each choice, that a person of ordinary skill in the art would have been required to make before arriving at entecavir. Nor did the court consider that a skilled artisan would have had to confront countless combinations and permutations of those choices. *See infra* pp. 56-57.

3. Reasonable expectation of success

The court next determined that "a person of skill in the art could have reasonably expected the substitution of a exocyclic methylene group at the [6] prime position of 2'-CDG to create a compound that had similar properties to 2'-CDG, including antiherpetic activity." A128. But when evaluating whether the skilled artisan would have had a reasonable expectation of success, the court did not consider its own findings that entecavir has several unexpected therapeutic

properties critical to its antiviral efficacy and safety. A150-151. Nor did the court consider that creating a compound with similar properties to 2'-CDG would mean creating a compound with high toxicity and potent antiherpetic activity—neither of which entecavir possesses. *See infra* pp. 35-36.

4. Objective considerations of nonobviousness

Turning to objective considerations, the court found the presence of several objective indicia of nonobviousness, including:

- *Commercial success.* The court found that Baraclude® is a commercial success in terms of revenues and market share and that BMS "sufficiently demonstrated a nexus between Baraclude's commercial success and entecavir, the invention covered by claim 8 of the '244 patent." A135-136.
- *Unexpected results.* The court found that entecavir has numerous unexpected therapeutic properties, including "extraordinary potency" against hepatitis B, "a very high genetic barrier to resistance," and "a large therapeutic window." A150-151.
- *Long-felt but unmet need.* Because hepatitis B "was considered an important worldwide disease" with no FDA-approved treatment available in 1990, the court found that "there was a long-felt need for a drug that

could be effective against hepatitis B at the time entecavir was invented." A147.

For other objective considerations, the court determined that the evidence did not strongly weigh in favor of nonobviousness:

- *Copying.* Although Teva admitted to copying, the court ruled that Teva's copying "does not amount to compelling evidence of nonobviousness" because the Hatch-Waxman regime encourages such copying. A132-133.
- *Skepticism.* The court acknowledged BMS's expert testimony regarding skepticism toward entecavir, but stated that it was "simply not enough to weigh in BMS's favor as to this factor regarding nonobviousness." A140.
- *Failure of others.* Stating that the "evidence does not paint a dramatic picture of failure in terms of effective treatments for hepatitis B," the court determined that the evidence "does not strongly support" a finding of failure of others. A143-144.

Then, despite recognizing the clear presence of several objective indicia of nonobviousness, the court disregarded those findings because it believed the evidence for other objective considerations "was not particularly compelling," such that BMS's overall showing on objective considerations was "mixed." A153.

SUMMARY OF ARGUMENT

Teva failed to prove by clear and convincing evidence that BMS's invention of entecavir was obvious. The district court's analysis, including its ultimate conclusion of obviousness, was flawed in three key respects.

First, the district court erred in concluding that a person of ordinary skill in the art would have had a reasonable expectation of success in obtaining the claimed invention. The court found that entecavir possesses several unexpected therapeutic properties, including "'extraordinary potency against' the hepatitis B virus," "a very high genetic barrier to resistance," and "a large therapeutic window" between the low doses necessary to treat hepatitis B and the high doses that can cause toxicity. A150-151. The court also recognized that, contrary to the expectation that 2'-CDG and entecavir would have "similar properties" (A128), there are substantial differences between the two compounds—"[t]he most significant" of which is "that the former is toxic while the latter is not" (A36-37(¶99)). Because "a compound and all of its properties are inseparable" for purposes of assessing obviousness, *Papesch*, 315 F.2d at 391, the court's recognition that entecavir possesses several *unexpected* therapeutic properties alone demonstrates that a skilled artisan would not have had a reasonable *expectation* of success in creating the claimed invention.

Second, the district court's multi-step obviousness analysis was impermissibly driven by hindsight. The court focused on the structural similarity between 2'-CDG and entecavir (a hindsight-driven comparison to begin with), while ignoring that even seemingly small changes to the chemical structure of a nucleoside analog often produced *unpredictable* results. The court then charted a course to the claimed invention involving at least six separate decisions, often making counterintuitive choices that run contrary to the teachings of the very prior art references that the court cited. But when the multiple options at each step along the court's path to the claimed invention are considered, it is clear that—without the benefit of hindsight—a skilled artisan would have faced a multitude of possibilities leading far away from entecavir. As a result, this case "clearly is not the easily traversed, small and finite number of alternatives that *KSR* suggested might support an inference of obviousness." *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1364 (Fed. Cir. 2008) (citation omitted). Rather, the district court's analysis "'has all the earmarks of somebody looking at this from hindsight.'" *Yamanouchi*, 231 F.3d at1345 (citation omitted).

Finally, the district court erred in its consideration of the objective evidence of nonobviousness. For example, although the court found strong evidence of unexpected results, the court erroneously discounted that evidence by comparing entecavir to tenofovir—a compound that was not even asserted as part of any prior

art obviousness combination—and by relying on the inventor's own expectations. The court then disregarded its findings of several objective indicia of nonobviousness (*i.e.*, unexpected results, long-felt but unmet need, and commercial success) because it believed that comparatively weaker evidence of other objective indicia (*i.e.*, skepticism and failure of others) made the overall evidence of objective considerations "mixed." A153. But that approach is precisely what this Court has described as an "improper trap of constructing a selective version of the facts relating to the objective considerations so as to confirm [the court's] hunch that the asserted claims were obvious." *Cyclobenzaprine*, 676 F.3d at 1080. Had the district court instead properly considered the strong objective evidence of entecavir's nonobviousness against Teva's affirmative case, it could not have found clear and convincing proof of obviousness.

ARGUMENT

I. STANDARD OF REVIEW

Because a patent is presumed valid, an accused infringer bears the burden of proving invalidity by clear and convincing evidence. *Microsoft Corp. v. i4i Ltd. P'ship*, 131 S. Ct. 2238, 2242 (2011). The burden of proving obviousness remains with the accused infringer at all times and never shifts to the patentee. *Cyclobenzaprine*, 676 F.3d at 1079-1080.

Obviousness is a question of law that is reviewed *de novo*, based upon underlying factual questions that are reviewed for clear error following a bench trial. *Honeywell Int'l, Inc. v. United States*, 609 F.3d 1292, 1297 (Fed. Cir. 2010). The underlying factual inquiries include: (1) the scope and content of the prior art; (2) the level of ordinary skill in the prior art; (3) the differences between the claimed invention and the prior art; and (4) objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966). It is legal error to evaluate those factual inquiries, or to reach an overall conclusion of obviousness, by relying upon hindsight reasoning. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007) ("A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning." (citation omitted)); *Cyclobenzaprine*, 676 F.3d at 1071 ("[C]ourts should reject 'hindsight claims of obviousness.'" (citation omitted)).

II. THE DISTRICT COURT ERRED IN CONCLUDING THAT CLAIM 8 IS INVALID AS OBVIOUS.

A. The District Court's Finding Of A Reasonable Expectation Of Success Cannot Be Reconciled With Its Findings That Entecavir Has Numerous *Unexpected* Therapeutic Properties.

To prove obviousness, an accused infringer must demonstrate by clear and convincing evidence not only that a skilled artisan would have been motivated to combine the teachings of the prior art to obtain the claimed invention but also "'that the skilled artisan would have had a reasonable expectation of success in

doing so.'" *Procter & Gamble Co. v. Teva Pharm. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009) (citation omitted).

That analysis requires consideration of "the claimed invention as a whole." 35 U.S.C. § 103. Consistent with that statutory mandate, this Court and its predecessor court have long recognized in the field of chemistry that "a compound and all of its properties are inseparable" for purposes of assessing obviousness. *Papesch*, 315 F.2d at 391; *see also Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1307 (Fed. Cir. 2011) ("Our case law is clear that the structure of a claimed compound and its properties are inseparable for purposes of § 103.").

As a result, unexpected therapeutic properties are particularly strong evidence of nonobviousness for chemical inventions. The reasonable *expectation* of success necessary to prove obviousness is unlikely to exist where the claimed compound possesses *unexpected* therapeutic properties. *See In re Rosuvastatin Calcium Patent Litig.*, 703 F.3d 511, 517-518 (Fed. Cir. 2012) (affirming nonobviousness where the claimed invention's unexpectedly superior properties "creat[ed] no reasonable expectation of success"); *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1361-1362 (Fed. Cir. 2007) (no reasonable expectation of success in light of the claimed invention's unexpected lack of toxicity); *Yamanouchi*, 231 F.3d at 1345 (no reasonable expectation of success

where a skilled artisan "would not have expected [the claimed invention] to have the most desirable combination of pharmacological properties that it possesses" (internal quotation marks omitted)). Indeed, BMS is not aware of a single case in which this Court has found a claim to a new chemical entity obvious where the claimed invention possessed unexpected therapeutic properties.

Here, the district court found—and Teva did not dispute—that entecavir has several unexpected therapeutic properties. A150-151 (finding that "[e]ntecavir has turned out to have certain attributes beyond what was expected at the time of the invention," including "'extraordinary potency against' the hepatitis B virus," "a very high genetic barrier to resistance," and "a large therapeutic window"). Those *unexpected* properties, which are "inseparable" from the claimed compound, demonstrate as a matter of law that a person of ordinary skill in the art would not have had a reasonable expectation of success in making the claimed invention.[5] *See Papesch*, 315 F.2d at 391 (holding that "[t]here is no basis in law for ignoring any property" when assessing obviousness); *see also Eli Lilly & Co. v. Zenith Goldline Pharm., Inc.*, 471 F.3d 1369, 1378 (Fed. Cir. 2006) (affirming district court's determination that the unexpected therapeutic properties of the claimed compound negated any reasonable expectation of success). Had the district court

[5] Of course, those unexpected results are also strong objective evidence of nonobviousness. *See infra* pp. 61-62.

considered its findings that entecavir possesses several unexpected therapeutic properties, it could not have found clear and convincing evidence of a reasonable expectation of success.[6]

In fact, the district court's findings confirm both that a person of ordinary skill in the art would not have expected all of entecavir's therapeutic properties and also that a skilled artisan's expectations about entecavir would have been incorrect. The court found that a skilled artisan "could have reasonably expected" entecavir to have "similar properties to 2'-CDG"—the alleged lead compound—"including antiherpetic activity." A128. Contrary to those expectations, 2'-CDG and entecavir have vastly different properties: 2'-CDG has more antiherpetic activity but also far greater toxicity. Indeed, the difference in toxicity is quite substantial, as the district court found. A36-37(¶99) ("The most significant difference between 2'-CDG and entecavir is that the former is toxic while the latter is not."). When testing 2'-CDG in woodchucks, which was the leading animal model for studying

[6] This Court's decision in *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348 (Fed. Cir. 2007), does not suggest otherwise. In holding the claimed invention obvious, this Court ruled that "Pfizer has simply failed to prove that the results are unexpected." *Id.* at 1371. Here, by contrast, the evidence of entecavir's unexpected results is undisputed. *See*, *e.g.*, A150 (noting testimony from Teva's expert acknowledging entecavir's unexpected potency). Moreover, in *Pfizer*, this Court relied heavily on the absence of any therapeutic benefit in finding the claimed invention obvious. 480 F.3d at 1368 (finding obviousness where "the acid addition salt formulation has no effect on the therapeutic effectiveness of the active ingredient and the prior art heavily suggests the particular anion used to form the salt"). Unlike in *Pfizer*, entecavir's unexpected properties relate to the drug's therapeutic performance.

hepatitis B, researchers "never found a dose that wasn't toxic." A1255(1010:5-6). By contrast, "there … wasn't any evidence of toxicity" for entecavir in woodchucks. A1258(1019:18-19). And although 2'-CDG has never been tested in humans due to its toxicity (A1255(1010:12-17)), entecavir has excellent safety in humans (A50-51(¶140); A1114(446:1-7)). Moreover, while 2'-CDG has high activity against the herpes virus, entecavir is only weakly active by comparison. *Compare* A103 (2'-CDG five to six times *more* potent than acyclovir against the herpes virus), *with* A16(¶41) (entecavir four times *less* potent than acyclovir against the herpes virus). Indeed, BMS initially chose not to put entecavir into clinical development because it was not active enough against the herpes virus in comparison to acyclovir, which was the standard at the time. A1210(828:16-829:9).

Although some of entecavir's unexpected therapeutic properties were not appreciated immediately upon entecavir's invention, they cannot be ignored when assessing obviousness. *See Knoll Pharm. Co. v. Teva Pharm. USA, Inc.*, 367 F.3d 1381, 1385 (Fed. Cir. 2004) ("There is no requirement that an invention's properties and advantages were fully known before the patent application was filed, or that the patent application contains all of the work done in studying the invention, in order for that work to be introduced into evidence in response to litigation attack."); *Papesch*, 315 F.2d at 391 (finding the claimed invention

nonobvious based upon unexpected properties discovered subsequent to filing the patent application because "[t]here is no basis in law for ignoring *any* property" in evaluating obviousness (emphasis added)); *see also Genetics Inst.*, 655 F.3d at 1307 ("[W]e have held that evidence of unexpected results may be used to rebut a case of *prima facie* obviousness even if that evidence was obtained after the patent's filing or issue date.").

Nor is there any significance to the district court's finding that 2'-CDG was not known to be toxic at the time of entecavir's invention, such that entecavir would have been expected to be safe. A30(¶87). As a matter of law, a reasonable expectation of success cannot rest on incorrect assumptions about the similarities between two compounds. *See Papesch*, 315 F.2d at 391 ("An assumed similarity based on a comparison of formulae must give way to evidence that the assumption is erroneous."). To hold otherwise would embrace precisely the type of results-driven reasoning that has no place in the obviousness analysis. And in this case, it would oddly suggest that a reasonable expectation of success could exist in 1990 when 2'-CDG's toxicity was not well-established, but not a few years *later* when 2'-CDG's toxicity was conclusively proven. Moreover, ignoring the difference in toxicity between 2'-CDG and entecavir is contrary to the statutory mandate that obviousness be measured with respect to "the claimed invention as a whole," 35 U.S.C. § 103, which for chemical compounds includes even

subsequently-discovered differences from the prior art. *See Genetics Inst.*, 655 F.3d at 1307. Had the district court considered *all* of entecavir's properties—including those that it recognized were unexpected—it could not have found any reasonable expectation of success, let alone by clear and convincing evidence. For this reason alone, the invalidity judgment should be reversed.

B. The District Court's Obviousness Analysis Was Improperly Driven By Hindsight.

To demonstrate the obviousness of a new chemical compound, an accused infringer must prove by clear and convincing evidence that "a chemist of ordinary skill would have selected the asserted prior art compounds as lead compounds, or starting points, for further development efforts." *Otsuka*, 678 F.3d 1291. A lead compound is "a compound in the prior art that would be most promising to modify in order to improve upon its … activity and obtain a compound with better activity." *Takeda*, 492 F.3d at 1357. The selection of a lead compound depends on its known properties, rather than its structural similarity to the claimed invention, focusing on whether "one of ordinary skill in the art would have had a reason to select a proposed lead compound or compounds over other compounds in the prior art." *Daiichi Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010). "Were it otherwise, the analysis would impermissibly rely upon *ex post* reasoning." *Otsuka*, 678 F.3d at 1292.

The accused infringer must also prove by clear and convincing evidence that "the prior art would have supplied one of ordinary skill in the art with a reason or motivation to modify a lead compound to make the claimed compound with a reasonable expectation of success." *Id.*; *see Takeda*, 492 F.3d at 1357. As with the selection of a lead compound, the relevant properties of the compounds known in the art guide the analysis, "for 'it is the possession of promising useful properties in a lead compound that motivates a chemist to make structurally similar compounds.'" *Otsuka*, 678 F.3d at 1292-1293 (quoting *Daiichi*, 619 F.3d at 1354).

Here, the district court's own analysis demonstrates the complexity of the problem solved by the inventors of the '244 patent—both in selecting a lead compound and in identifying the appropriate structural modifications to make to that compound. The court's path to the claimed invention involved at least six decisions, with each step presenting difficult choices among multiple reasonable alternatives with unpredictable results. When all of the possible combinations and permutations are considered, those choices multiply into countless possibilities facing a skilled artisan, and any misstep along the way would have led far afield from the claimed invention.

To arrive at the claimed invention, the district court repeatedly made counterintuitive choices that conflicted with the teachings of the same prior art references it relied upon to find the invention obvious. Such an analysis "'has all

the earmarks of somebody looking at this from hindsight.'" *Yamanouchi*, 231 F.3d at 1345 (citation omitted); *see also Otsuka*, 678 F.3d at 1296 (rejecting a complex, multi-step obviousness analysis as "a poster child for impermissible hindsight reasoning"). Because the district court erred as a matter of law in relying on hindsight at every turn, the court's invalidity judgment should be reversed.

1. The district court's choice of a lead compound was based on hindsight.

a. The counterintuitive choice of carbocyclics over the well-known, safe, effective, and easy-to-synthesize furanosides and acyclics

The district court recognized that there were three broad classes of nucleoside analogs that a person of ordinary skill in the art would have considered as possible lead compounds: furanosides, acyclics, and carbocyclics. A18(¶48). Although the court determined that a skilled artisan would have selected a carbocyclic as the starting point for developing a new antiviral drug (A97), the court's own factual findings demonstrate that furanosides and acyclics were far more promising potential leads.

As the district court found, furanosides and acyclics were both known to be potent antiviral drugs by the late 1980s. A93 (furanosides and acyclics "had good antiherpetic track records by the 1980s"). In fact, there were several furanosides and acyclics that were FDA-approved, or well on their way to FDA approval, as antiviral treatments at the time of the invention in 1990. *E.g.*, A18(¶49) (*ara*-A);

A19(¶52) (acyclovir); A19(¶55) (ganciclovir). By contrast, although carbocyclics had been studied since the 1960s (A95), no carbocyclic had FDA approval at the time of entecavir's invention (A20(¶59)). And at least one reference relied upon by the district court directly disparaged the antiviral activity of carbocyclics as compared to the well-established efficacy of furanosides. A2091 ("[C]arbocyclic versions of anti-viral nucleosides have been found to be less active than their furanose parents.").

Presented with the well-documented safety and efficacy of furanosides and acyclics, a person of ordinary skill in the art naturally would have selected one of those classes of compounds for further development, particularly where decades of carbocyclic research had resulted in no FDA-approved drugs. *See Otsuka*, 678 F.3d at 1293 (finding that a particular class of compounds were "not plausible lead compounds, except in retrospect," where none were marketed for the treatment of the targeted disease at the time of the invention); *Daiichi*, 619 F.3d at 1353-1354 (concluding that a person of ordinary skill in the art would favor several classes of lead compounds that "had been more thoroughly studied" over the class of lead compounds proposed by the accused infringer). Indeed, that is exactly what the inventors did here, starting their research with acyclovir (an acyclic) before focusing on oxetanocin-A (a furanoside), which ultimately led to the discovery of entecavir. *See supra* pp. 16-18. And, as the district court found, the inventors

were not alone in making that choice. *E.g.*, A19-20(¶56) (observing that "there were plenty of researchers who were still using acyclic nucleoside analogs as lead compounds" at the time of the invention). Only through impermissible hindsight is it possible to make the counterintuitive choice to select the unproven class of carbocyclics over the demonstrated safety and efficacy of furanosides and acyclics.[7]

Apart from the established therapeutic superiority of furanosides and acyclics, there were compelling practical reasons to select furanosides or acyclics over carbocyclics. As the district court observed, "[f]uranosides are straightforward to synthesize" (A19(¶50)) and "acyclics are easy to make" (A19(¶53)). By contrast, "[c]arbocyclics take a long time to synthesize." A20(¶60). Again, only guided by hindsight would a skilled artisan go against the teachings of the prior art and choose the more difficult path—particularly where there were more readily obtainable alternatives.

The district court acknowledged that "it is possible that the skilled artisan may have chosen other lead compounds," including furanosides and acyclics. A93-94. The court, however, failed to consider any of those other lead compounds

[7] The district court's singular focus on carbocyclics is no doubt attributable to the hindsight bias relied on by Teva's expert Dr. Heathcock, who confined his analysis to the materials selected by Teva's attorneys rather than materials gathered through independent analysis. A1073-1075(287:2-295:23).

because the prior art need not "point to only a single lead compound." A93 (quoting *Altana Pharma AG v. Teva Pharm. USA, Inc.*, 566 F.3d 999, 1008 (Fed. Cir. 2009)). But by ignoring those other potential lead compounds, the court effectively bypassed the required step of "select[ing] a proposed lead compound or compounds *over other compounds* in the prior art." *See Daiichi*, 619 F.3d at 1354 (emphasis added). At the very least, the court erred as a matter of law in finding the claimed invention obvious to try (A112-127) by failing to consider the other possible lead compounds that it recognized a skilled artisan might select. *See infra* pp. 56-57.

b. The hindsight-driven choice of 2'-CDG over other more potent carbocyclics disclosed in the same references

From the outset, the district court's selection of 2'-CDG from among the broad class of carbocyclics impermissibly rested on hindsight. Rather than starting with 2'-CDG's known properties, the court began its analysis by assessing the structural similarity between 2'-CDG and entecavir. A97-102. Although structural similarity can provide a *motivation to modify* a lead compound, *see*, *e.g.*, *In re Mayne*, 104 F.3d 1339, 1343 (Fed. Cir. 1997), it cannot be a reason to *select* a lead compound in the first place. *Otsuka*, 678 F.3d at 1292 ("[M]ere structural similarity between a prior art compound and the claimed compound does not inform the lead compound selection."); *see Daiichi*, 619 F.3d at 1354. But the

district court did precisely that here, selecting a lead compound by starting from the very solution that the inventors discovered. A97-102.

The district court's analysis of 2'-CDG's known properties was also tainted by hindsight. The court recognized that "[t]he case law emphasizes that compounds called out in the prior art as exhibiting the highest potency and/or activity are the most likely leads." A103 (citing *Otsuka*, 678 F.3d at 1294). But the court did not apply that principle to this case, overlooking far more potent antiviral carbocyclics described in the very prior art references underlying its obviousness analysis. Even the Montgomery article, which Teva's expert touted as "a lamp post that really illuminates 2'CDG as – as a very exciting lead compound to work from" (A1049(191:9-10)), actually identifies another carbocyclic compound (C-DAPdR) as twice as potent as 2'-CDG. *See* A2149 (Fig. 4) (minimum effective antiviral concentration of C-DAPdR is 0.05 μg/mL versus 0.11 μg/mL for 2'-CDG). And another prior art reference describes a different carbocyclic that demonstrated "unprecedented biological activity," which was particularly "noteworthy" as compared with the "much less active" 2'-CDG. A2091.

If anything, a person of ordinary skill in the art would have been motivated to select one of the several carbocyclics known to be improvements upon 2'-CDG, not to forgo those benefits by starting with 2'-CDG instead. *See Daiichi*, 619 F.3d

at 1356 (rejecting proposed lead compounds where other modified versions of those compounds had greater potency); *Yamanouchi*, 231 F.3d at 1345 ("If activity alone was the sole motivation, other more active compounds would have been the obvious choices …."). Only by relying on hindsight could the district court select 2'-CDG as a lead compound over the prior art teachings identifying other far more potent carbocyclics.

Although BMS's expert Dr. Schneller acknowledged that 2'-CDG would be "on the list" of possible lead compounds for antiviral research in the late 1980s (A1282(1111:7-12)), that does not suggest that a skilled artisan would have been more apt to choose 2'-CDG over the many other compounds known to have antiviral activity at the time. As the court recognized (A27-28(¶81)), Dr. Schneller made clear that there were "hundreds" of compounds that would be on the list of potential lead compounds. A1282(1111:13-16); *see*, *e.g.*, A2102-2105 (listing over 120 different carbocyclics); A2144-2152 (disclosing 60 different carbocyclics). Indeed, Dr. Shealy, who discovered 2'-CDG, recognized at the time that numerous carbocyclics had potent antiviral activity. A2067 ("Most of these compounds are highly active.").

Nor was the district court correct to select 2'-CDG as a lead compound merely because other researchers in the late 1980s were using 2'-CDG in their research. A107-111. If anything, the fact that none of those researchers arrived at

entecavir confirms that the district court erred in finding the claimed invention obvious to try. *See infra* pp. 57-58. Moreover, 2'-CDG was not the only carbocyclic that others were using at the time. Researchers, including those at BMS, were studying potent carbocyclics with vastly different structures from 2'-CDG, such as lobucavir, which has only four (rather than five) carbons in its carbocyclic ring. A1224(884:10-885:24) (lobucavir independently discovered by scientists at BMS, Abbott Laboratories, and Nippon Kayaku); A2207 (describing the antiviral activity of lobucavir (SQ-33054) as "superior to acyclovir, and comparable to ganciclovir"); A2217 (showing the structure of lobucavir); *see also* A2130 (praising three carbocyclics with significantly different structures from 2'-CDG as "[h]ighlighting the antiviral usefulness of carbocyclic nucleosides"). The district court erred as a matter of law by relying on hindsight to ignore those other carbocyclics as potential lead compounds. *See Daiichi*, 619 F.3d at1354 ("[T]he attribution of a compound as a lead compound after the fact must avoid hindsight bias ….").

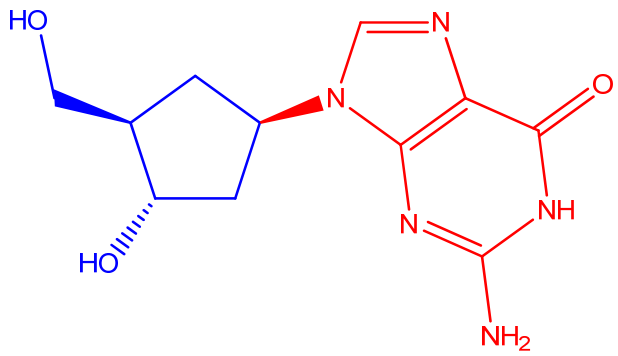
2. The district court's multi-step analysis of the structural modifications necessary to create the claimed invention rests on hindsight.

Even assuming that a skilled artisan would have selected 2'-CDG as a lead compound, there was no clear path from that starting point to the claimed invention. To the contrary, the complexity of the court's own analysis—with

multiple additional decision points, each of which involved a choice among many reasonable alternatives with unpredictable results—only highlights the court's improper reliance on hindsight. *See Otsuka*, 678 F.3d at 1296; *Ortho-McNeil*, 520 F.3d at 1364; *Yamanouchi*, 231 F.3d at 1345.

a. The choice of modifying 2'-CDG's carbocyclic ring rather than one of several modifications to its guanine base known to produce highly active antiviral compounds

Starting with 2'-CDG as a lead compound, the first choice that a person of ordinary skill in the art would have had to make—if they would have chosen to modify it at all[8]—is whether to modify the compound's carbocyclic ring (shown in blue), guanine base (shown in red), or both:



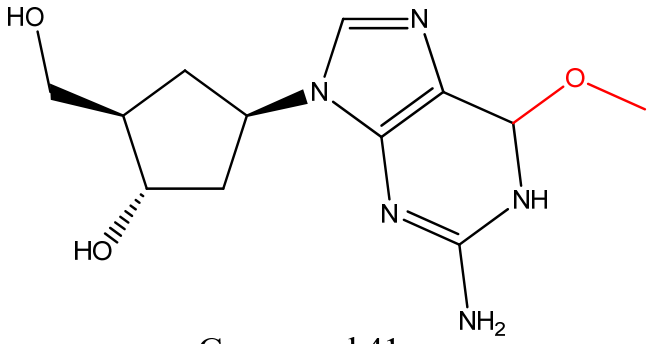
See A113-115. Although the court acknowledged that "[t]here appears to have been no reference in any prior art explicitly stating that changes to the guanine base must be avoided" (A114), the court nevertheless found that a skilled artisan

[8] If, as the district court found (A103), 2'-CDG itself has desirable antiviral properties, it is not clear why a person of ordinary skill in the art would have been motivated to modify it at all.

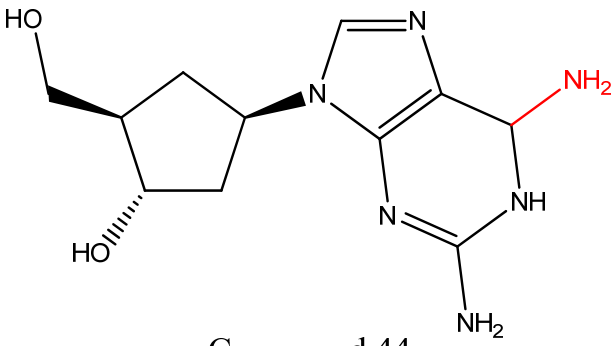
would have focused "on the sugar portion of 2'-CDG" in making modifications to that lead compound (A115).

The court's focus on 2'-CDG's carbocyclic ring relied heavily on a single prior art reference ("the Harnden and Jarvest article") supposedly showing that modifications to the guanine base resulted in reduced efficacy. A114 & n.27 (citing A2010). That finding is clearly erroneous. Although the Harnden and Jarvest article does indicate that modifications to the guanine base for certain analogs of acyclovir had resulted in reduced antiviral activity (A2010), the authors of the article also synthesized several base-modified compounds that showed a "high degree of activity" (A2012). Not only were the authors impressed by the "potent antiviral activity" of a particular base-modified compound that they had created, but the success of that modification to the guanine base "encouraged" them to synthesize and evaluate other compounds having the same modification to the base. *Id.*

Other prior art references relied upon by the district court likewise show that modifications to the guanine base resulted in compounds with potent antiviral activity. For example, the Montgomery article at the heart of Teva's obviousness case specifically calls attention to two *base*-modified derivatives of 2'-CDG:



Compound 41



Compound 44

A2148. Compound 41 has a methoxy group (OCH_3) (shown in red) substituted on the guanine base, while compound 44 has an amino group (NH_2) (shown in red) substituted on the guanine base. *Id.* Rather than discouraging modifications to the guanine base, the Montgomery article describes compounds 41 and 44 as among "the most promising carbocyclic purine nucleosides for the treatment of herpes infections." *Id.*; *see also* A2149 (compound 44 (C-DAPdR) is twice as potent as 2'-CDG). And at least one reference relied upon by the district court actually discourages modifications to the carbocyclic ring. A2130 (explaining that carbocyclics "whose structure depart[s] significantly from that of a sugar moiety" are "generally ineffective"). Only in retrospect is it possible to conclude that a skilled artisan would overlook the references disclosing highly active antiviral agents with modifications to the base and modify 2'-CDG's carbocyclic ring instead, even in the face of references directly discouraging such changes.

b. The choice of modifying the 6'-position over other well-studied locations to modify the carbocyclic ring

Even if a person of ordinary skill in the art would have chosen to modify 2'-CDG's carbocyclic ring, there were multiple locations that a skilled artisan might have selected to modify, as the court itself found. A115. Although the prior art teaches modifications at several locations (*e.g.*, A2102-2103 (listing dozens of compounds with modifications at the 2'- and 3'-positions, but none at the 6'-position); A2008 (compound 2 contains a substitution at the 4'-position)), the court found that a person of ordinary skill in the art would have selected either the 2'- or 6'-position because those locations contained no substituents that might already contribute to 2'-CDG's biological activity. A115.

But even as between the 2'- and 6'-positions, neither the district court nor Teva's expert attempted to explain why a skilled artisan would have been motivated to select the 6'-position. A115; A1052(202:5-8). Nor could they, as the prior art references relied upon by Teva and the court specifically teach that modifications to the *2'-position* of 2'-CDG substantially increase its antiviral potency. A2091 (finding that adding a fluorine to the 2'-position of 2'-CDG created a compound with "unprecedented biological activity," particularly as compared to the "much less active" unmodified 2'-CDG). Again, only with the benefit of hindsight would a person of ordinary skill in the art ignore the

demonstrated antiviral benefits of modifying the 2'-position of 2'-CDG and modify the untested 6'-position instead.

c. The choice of a carbon-based substituent over the numerous other elements successfully used to modify carbocyclic compounds

Even if a person of ordinary skill in the art would have chosen to modify the 6'-position of 2'-CDG, the district court recognized that he or she would have had to consider the multiple possibilities reflected in the periodic table itself in deciding *how* to modify the 6'-position. A116. The court stated that "the skilled artisan would focus on the top row of the table, as that contains the smallest elements." A117. That determination, however, cannot be reconciled with the prior art references cited by Teva and the court, which disclose modifications using elements from outside the first row of the periodic table. *E.g.*, A2008 (compound 1f contains a sulfur-based modification at the 2'-position of the sugar ring); A2119 (disclosing carbocyclics with iodine, bromine, chlorine, and sulfur-based substitutions at the 2'-position of the carbocyclic ring); A2144 (disclosing carbocyclics with chlorine, bromine, and sulfur-based substitutions). The Shealy patent itself—which discloses and claims 2'-CDG—identifies modifications to carbocyclics utilizing elements from outside the first row of the periodic table. A2084 (Table 1) (showing antiviral activity of carbocyclics modified by sulfur and chlorine).

Nevertheless, even with the court's narrow focus on the first row of the periodic table, there were several reasonable modifications that a skilled artisan would have considered. A1053(206:5-7) (Heathcock) ("A medicinal chemist really would focus in on carbon and fluorine …."); A1304(1199:7-10) (Schneller) (identifying carbon, oxygen, nitrogen, and fluorine as elements from the first row of the periodic table that could be added to 2'-CDG). Although the court found that carbon and fluorine were the two elements that a person of ordinary skill in the art would most likely use to modify the carbocyclic ring (A117), the prior art relied upon by Teva and the court discloses substitutions to the carbocyclic ring involving other elements from the first row of the periodic table. *E.g.*, A2102-2103 (disclosing 80 nucleoside analogs containing modifications to their carbocyclic rings involving nitrogen, oxygen, and hydrogen, but not carbon or fluorine). Only in hindsight would a skilled artisan focus on just carbon and fluorine when considering what modifications to make to 2'-CDG.

d. The choice of adding a 6'-methylene group as in the highly toxic Madhavan compound 30 over the numerous alternative carbon-based groups

Even if a person of ordinary skill in the art had decided to modify the 6'-position of 2'-CDG with a carbon substituent, the choice of adding a methylene group (*i.e.*, a carbon attached by a double bond) was far from obvious. Only the Madhavan article (A2001-2007)—one reference out of the dozens considered by

the court—teaches the addition of a methylene group at the 6'-position of a carbocyclic ring. A1207(815:21-816:9) (explaining that the addition of a 6'-methylene group was not "routine" at the time of entecavir's invention). If the addition of a 6'-methylene group were truly an obvious modification, there undoubtedly would be more than a single reference from the decades of nucleoside analog research disclosing it. *See Daiichi*, 619 F.3d at 1355 (rejecting supposed motivation to modify a lead compound where "few compounds" in the prior art disclosed the necessary modifications to obtain the claimed invention); *Procter & Gamble*, 566 F.3d at 997 (finding no motivation to modify a lead compound where "there [was] no credible evidence that the structural modification was routine").

Indeed, the selection of a methylene group would have been counterintuitive because the Madhavan article discloses a methylene substitution at the 6'-position that resulted in a compound described as "[t]he most potent, *but also the most toxic*." A2003 (emphasis added). And, in the very next line, the Madhavan article explains that there were other modifications that could be made to the 6'-position that resulted in a compound that was "*nearly as active and much less toxic*." *Id.* (emphasis added). Only through hindsight would a skilled artisan select a modification—not known elsewhere in the art—that resulted in increased toxicity, particularly where there were known alternatives that "were much less toxic" without significantly sacrificing potency.

Dr. Schneller's testimony that carbon "sticks out" as the most conservative modification that a skilled artisan could make (A1304-1305(1200:1-1203:3)) is not inconsistent with that conclusion. Dr. Schneller's testimony concerned the addition of a single-bonded methyl group (CH_3), not a double-bonded methylene group (CH_2). A1304(1200:21-24). As Dr. Schneller testified, a double-bonded methylene group restricts the molecule's flexibility and shape much more than a single-bonded methyl group, which makes the addition of a methylene group a significant change to the compound's structure. A1273(1082:7-13) (explaining that "there is a lot less flexibility" in a carbocyclic ring following the addition of a double-bonded methylene group); A1281(1106:3-23) (explaining that the double bond in entecavir restricts the shape of the carbocyclic ring).

Nor was the district court correct to find it obvious to make a 6'-methylene substitution based upon Dr. Schneller's statement that the high toxicity of Madhavan's compound 30 "might not dissuade a person of ordinary skill in the art from making a molecule with a 6' exocyclic methylene group." A122-124 (emphasis omitted); A2185; *see also* A1311-1312(1228:8-1280:14). In context, Dr. Schneller was merely opining that a person of ordinary skill in the art likely would not consider the Madhavan compounds at all because they work against different enzymatic targets and by a different mechanism than antiviral agents like 2'-CDG. A2184-2185; *see also* A1285-1287(1124:5-1131:5). If a skilled artisan

would not consider the Madhavan compounds at all, their toxicity would not influence that person one way or the other in trying to develop new antiviral agents from 2'-CDG. To the extent a skilled artisan might find the Madhavan article relevant, Dr. Schneller was clear that "[t]his mechanism of antiviral activity through toxicity to the host would certainly not suggest that one of ordinary skill in the art should make an antiviral molecule with a 6' exocyclic methylene group." A2185.

In any event, the addition of a methylene group was not the only carbon-based substitution that a person of ordinary skill in the art would have considered. For example, Teva's expert Dr. Heathcock testified that a medicinal chemist would "certainly" consider a methyl substitution (*i.e.*, a carbon attached by a single bond) as an alternative, since it is only "a little bit bigger" than a methylene group (*i.e.*, a carbon attached by a double bond). A1053(208:12-209:6). The prior art relied upon by Teva and the court confirm that others at the time were in fact modifying nucleoside analogs by adding methyl groups to the sugar ring. *E.g.*, A2020 (compounds 4, 5, 6, and 7 contain 2'-methyl substitutions). The court nevertheless determined that "the skilled artisan would pursue the addition of an exocyclic methylene group at either the 2 prime or [6] prime positions before she would think to add a methyl group." A117 n.30. The primary basis for that conclusion was that a methylene group is smaller than a methyl group. *Id.* But there was no

evidence offered at trial that size would be the determining factor in the choice of substituents. To the contrary, the prior art relied upon by Teva and the court disclosed substitutions on the sugar ring that are significantly larger than a methylene or methyl group. *E.g.*, A2025 (disclosing the synthesis of compounds with four different multi-carbon groups substituted at the 2'-position of the sugar ring). Only in hindsight could the district court ignore those other possible carbon-based modifications, which are disclosed in the very prior art references that the court relied upon to find the claimed invention obvious.

3. The district court ignored the many possibilities reflected in its own analysis to find the claimed invention obvious to try.

As the district court's own analysis confirms, the inventors of the '244 patent faced a complex problem with multiple, unpredictable steps along the path to a solution. That "clearly is not the easily traversed, small and finite number of alternatives that *KSR* suggested might support an inference of obviousness." *Ortho-McNeil*, 520 F.3d at 1364. Nevertheless, the court found claim 8 "obvious to try." A118-127. That was error for two reasons.

First, the court clearly erred in determining that a skilled artisan would have had only "six options to pursue" when developing entecavir. A117. The six supposed options—a single fluorine substitution above or below the sugar ring or a methylene substitution at the 2'- or 6'-position—concern only the last steps of the

court's obviousness analysis.[9] The court ignored the other steps, including: the choice among three broad classes of nucleoside analogs; the choice of 2'-CDG as a lead compound out of hundreds of possible carbocyclics; the choice of whether to modify 2'-CDG's guanine base, carbocyclic ring, or both; and the choice of which carbon on the carbocyclic ring to modify. When all of the combinations and permutations of choices along the path to the claimed invention are considered, the options quickly multiply to countless possibilities, taking this case well outside the "small," "finite," and "easily traversed" number of possibilities that could support a finding of obviousness. *Cyclobenzaprine*, 676 F.3d at 1072 ("Evidence of obviousness, especially when that evidence is proffered in support of an 'obvious-to-try' theory, is insufficient unless it indicates that the possible options skilled artisans would have encountered were 'finite,' 'small,' or 'easily traversed,' and that skilled artisans would have had a reason to select the route that produced the claimed invention." (quoting *Ortho-McNeil*, 520 F.3d at 1364)); *see also Takeda*, 492 F.3d at 1359 (rejecting argument that the claimed invention was obvious to try where "the prior art disclosed a broad selection of compounds any one of which could have been selected as a lead compound for further investigation"). Indeed,

[9] As explained (*see supra* pp. 55-56), even the last decision in the court's analysis involved a choice among more than six alternatives because there were numerous carbon-based substitutions other than a methylene group disclosed in the prior art that a skilled artisan would have had to consider.

the fact that several other scientists were actually using 2'-CDG in their research over the course of *six years* before the discovery of entecavir (A107-111), but none arrived at the claimed invention (A1085-1086(334:16-338:8)), suggests that entecavir was not merely one of a finite number of possibilities that a person of ordinary skill in the art might have tried. *See Rosuvastatin*, 703 F.3d at 518 (rejecting argument that the claimed invention was obvious to try where others had worked with the same class of compounds but not arrived at the claimed invention).

Second, an invention is obvious to try only when it is one of "a finite number of identified, *predictable* solutions." *KSR*, 550 U.S. at 421 (emphasis added). As the court's own findings demonstrate, there was nothing predictable about the claimed invention. Not only did the court find that the claimed invention possesses several *unexpected* therapeutic properties (A150-151), but contrary to the finding that a skilled artisan would have expected entecavir to have "similar properties to 2'-CDG" (A128), the court also found that the two compounds are vastly different. As the court noted, "[t]he most significant difference between 2'-CDG and entecavir is that the former is toxic while the latter is not." A36-37(¶99). And although 2'-CDG has strong antiherpetic activity, entecavir is only weakly active against the herpes virus by comparison. *Compare* A103 (2'-CDG five to six times

more potent than acyclovir against the herpes virus), *with* A16(¶41) (entecavir four times *less* potent than acyclovir against the herpes virus).

Moreover, the undisputed evidence demonstrates that even small changes to nucleoside analogs resulted in significant and unpredictable changes in their biological activity, as the witnesses for both parties testified. *See* A1041(161:5-15) (Heathcock) (explaining that the furanoside *ara*-A differs from the natural nucleoside adenosine only in the orientation of a single hydroxyl group (OH), but unlike the natural nucleoside, *ara*-A has potent antiviral activity); A1058(228:18-229:2) (Heathcock) (acknowledging that it is not possible "to accurately predict the precise activity … of a nucleoside analog ahead of time"); A1204(805:10-15) (Zahler) (explaining how "in the world of nucleosides …. [s]mall changes make what to traditional medicinal chemists would be considered inexplicably drastic changes in activity"); A1270-1271(1069:16-1071:14) (Schneller) (describing the unpredictable biological activity of nucleoside analogs, which is due to their interaction with various biological processes). Even the Madhavan article reflects the unpredictability of this area of chemistry. A2003 (compound 24 nine times less active than compound 10, which has the *same* chemical formula but differs only in the spatial orientation of a single fluorine atom). The unpredictability of these seemingly small changes—which are well-documented in the prior art and illustrated by the very facts of this case—takes the claimed invention well outside

the realm of known, predictable solutions that might support a finding of obviousness. *See Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d 1075, 1090 (Fed. Cir. 2008) (rejecting argument that the claimed invention was obvious to try where its properties were not predictable).

C. The District Court Erroneously Disregarded Its Own Findings Concerning Objective Considerations Of Nonobviousness.

To avoid precisely the type of hindsight reasoning that the district court engaged in here, this Court requires objective evidence of nonobviousness to be considered before making a determination on obviousness. *See Cyclobenzaprine*, 676 F.3d at 1075-1076; *Transocean Offshore Deepwater Drilling, Inc. v. Maersk Contractors USA, Inc.*, 617 F.3d 1296, 1305 (Fed. Cir. 2010) ("[A] district court must *always* consider any objective evidence of nonobviousness presented in a case."). This Court has repeatedly recognized that "'evidence of secondary considerations may often be the most probative and cogent evidence in the record.'" *Cyclobenzaprine*, 676 F.3d at 1075 (citation omitted); *see also Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1379 (Fed. Cir. 2012) ("Obviousness requires a court to walk a tightrope blindfolded (to avoid hindsight)—an enterprise best pursued with the safety net of objective evidence.").

Here, the court found several objective indicia of nonobviousness. The court found that "[e]ntecavir has turned out to have certain attributes beyond what was expected at the time of the invention" (A150), including "'extraordinary potency

against' the hepatitis B virus" (*id.*), "a very high genetic barrier to resistance" (A151), and "a large therapeutic window" (*id.*). Moreover, with "no FDA-approved drug for the treatment of hepatitis B" available in 1990, the court found that "there was a long-felt need for a drug that could be effective against hepatitis B at [the] time entecavir was invented." A147. In addition, because "Baraclude's sales performance has shown steady, significant growth," which has resulted in Baraclude® obtaining a "significant" share of the market "for most of the years since its launch," the court determined that the claimed invention has been a commercial success. A138.

Those findings demonstrate that Teva failed to meet its burden of providing clear and convincing evidence of obviousness. This Court has long recognized that unexpected results are particularly strong evidence of nonobviousness in the chemical field, "where minor changes in a product or process may yield substantially different results." *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995). Accordingly, unexpected results alone—particularly unexpected results bearing on the therapeutic properties of the claimed compound, as here—can negate any

affirmative evidence of obviousness.[10] *See Sanofi-Synthelabo*, 550 F.3d at 1089-1090 (affirming nonobviousness based on the "unexpected and unpredictable" properties of the claimed invention); *Soni*, 54 F.3d at 750-751 (finding evidence of unexpected results sufficient by itself to demonstrate the nonobviousness of the claimed invention); *In re Chupp*, 816 F.2d 643, 646-647 (Fed. Cir. 1987) (same); *In re May*, 574 F.2d 1082, 1093 (C.C.P.A. 1978) (same). When the several unexpected results found by the court are viewed in combination with the court's findings of other objective indicia, those findings together overwhelmingly show that Teva failed to carry its burden of offering clear and convincing evidence of obviousness.

Moreover, the district court's legal errors actually caused the court to *understate* the objective indicia of nonobviousness. For example, the court discounted the evidence of unexpected results because entecavir has similar

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[10] The unexpected therapeutic properties in this case are vastly different from the unexpected results that this Court found insufficient to defeat a finding of obviousness for the formulation claims in *Allergan, Inc. v. Sandoz Inc.*, ___ F.3d ___, 2013 WL 1810852 (Fed. Cir. May 1, 2013). In *Allergan*, the unexpected results related to a particular dosing regimen for the drug, not the claimed formulation itself. *Id.* at *2, 6. As a result, this Court found those unexpected results not "meaningful to [its] analysis of the formulation claims." *Id.* at *6. By contrast, this Court found the related method claims directed to the dosing regimen *not* obvious. *Id.* at *7. As with the nonobvious method claims in *Allergan*, entecavir's unexpected results relate directly to the subject matter claimed in claim 8 of the '244 patent and are particularly strong evidence of nonobviousness because a compound and its properties are "inseparable" when assessing obviousness. *Papesch*, 315 F.2d at 391.

properties to tenofovir—a later-approved therapy for hepatitis B. That was error because unexpected results are measured against the *closest* prior art. *See Kao Corp. v. Unilever U.S., Inc.*, 441 F.3d 963, 970 (Fed. Cir. 2006). Tenofovir was never offered as part of any prior art obviousness combination—let alone the closest prior art—to entecavir, and its properties relative to entecavir are therefore irrelevant to the issue of unexpected results. Moreover, the court relied heavily on the inventor's own expectations to discount BMS's evidence of unexpected results. *E.g.*, A149 (relying on the inventor's expectations as to entecavir's antiviral properties to determine what a person of ordinary skill in the art would have expected). Obviousness, however, depends upon the expectations of a person of ordinary skill in the art, *not* those of the inventor. *Standard Oil Co. v. Am. Cyanamid Co.*, 774 F.2d 448, 454 (Fed. Cir. 1985) ("[O]ne should not go about determining obviousness under § 103 by inquiring into what *patentees* (i.e., inventors) would have known or would likely have done."). Reliance on the inventor's own expectations is forbidden because they are presumed to be different from those of a person of ordinary skill in the art. *Id.* ("Inventors, as a class, according to the concepts underlying the Constitution and the statutes that have created the patent system, possess something … which sets them apart from the workers of *ordinary* skill."). The district court's own analysis in this case bears this out. *E.g.*, A128 n.35 (finding that the inventors approached the problem of

drug development in a way that "a person of ordinary skill in the art would not typically be thinking of").

Additionally, the court applied a legally erroneous standard by disregarding its own findings of several objective indicia demonstrating nonobviousness based upon a perceived weaker showing with respect to other objective indicia. A153. But this Court has rejected precisely that type of selective analysis of the objective evidence:

> The district court appears to have fallen into the understandable but improper trap of constructing a selective version of the facts relating to the objective considerations so as to confirm its hunch that the asserted claims were obvious. The district court focused on objective evidence that supported its obviousness determination, but ignored other evidence that cast the objective considerations in a light favorable to [the patentee].

Cyclobenzaprine, 676 F.3d at 1080. In other words, the absence of certain objective indicia does not *negate* the presence of others. Rather, the presence of each objective factor of nonobviousness must be given due weight in the overall obviousness analysis—such that even a single objective factor on its own can demonstrate nonobviousness. *See*, *e.g.*, *Soni*, 54 F.3d at 750-751 (finding the claimed invention nonobvious based upon unexpected results alone); *Chupp*, 816 F.2d at 646-647 (same); *May*, 574 F.2d at 1093 (same). Had the district court here properly considered its own findings of unexpected results, long-felt but unmet

need, and commercial success against Teva's affirmative case, it could not have found clear and convincing proof of obviousness.

CONCLUSION

The invalidity judgment should be reversed and the case remanded for further proceedings on remedies in the district court.

Respectfully submitted,

/s/ William F. Lee

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CERTIFICATE OF SERVICE

I hereby certify that I filed the foregoing Brief for Plaintiff-Appellant Bristol-Myers Squibb Company with the Clerk of the United States Court of Appeals for the Federal Circuit via the CM/ECF system this 3d day of June, 2013, and served a copy on counsel of record by the CM/ECF system and by electronic mail to the parties on the service list below.

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CERTIFICATE OF COMPLIANCE

Pursuant to Federal Rule of Appellate Procedure 32(a)(7)(C), the undersigned hereby certifies that this brief complies with the type-volume limitation of Federal Rule of Appellate Procedure 32(a)(7)(B)(i).

1. Exclusive of the exempted portions of the brief, as provided in Federal Rule of Appellate Procedure 32(a)(7)(B)(iii) and Federal Circuit Rule 32(b), the brief contains 13,639 words.

2. The brief has been prepared in proportionally spaced typeface using Microsoft Word 2010 in 14 point Times New Roman font. As permitted by Federal Rule of Appellate Procedure 32(a)(7)(C), the undersigned has relied upon the word count feature of this word processing system in preparing this certificate.

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